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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,010	FREY ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/20/2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32 and 36-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *47 and 48* is/are allowed.

6)☒ Claim(s) *29,30,32,37-45 and 49-51* is/are rejected.

7)☒ Claim(s) *31,36 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Pri rity under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of claims 30 and 40 and the addition of claims 47-51, Paper of 10/20/2003, is acknowledged. Claims 29-32, and 36-51 are still at issue and are present for examination.

Applicants' arguments filed on 10/20/2003, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 31, 36, 46 are objected to because of the following informalities:

Claims 31, 36 and 46 are dependent from rejected claims 30, 29, and 37 respectively.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 30, 32, 37-45 and 49-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was originally stated in the previous office action. In response to this rejection applicants have amended claims 30 and 40 and traverse this rejection as it applies to the amended claims.

Applicants continue to traverse this rejection on the basis that applicants disclosure of eight previously unknown amino acid sequences for lysine 2,3-aminomutase enzymes provides a structure to function/activity relationship between the species that demonstrates applicants possession of all possible lysine 2,3-aminomutases. Applicants submit that the disclosure of these eight species readily reveal unique amino acid motifs that serve to identify all lysine 2,3-aminomutases. Applicants argument is not found persuasive on the basis that applicants disclosure of eight species of the claimed genus is not sufficient to put applicants in possession of all enzymes having lysine 2,3-aminomutase activity, regardless of the source or structure of enzyme.

Applicants argument is not found persuasive because as was previously stated, claims 29, 30, 32, 37-45 are directed to all possible methods of producing L-□-lysine comprising any expression vector that encodes any lysine 2, 3-aminomutase in the presence of L-lysine (claims 29, 37, 42, 43, 44, 45), incubating L-lysine in the presence of any lysine 2, 3-aminomutase (claim 30, 32, 38, 39) or contacting L-lysine with any lysine 2, 3-aminomutase immobilized on a suitable support (claims 40, 41).

The mere contemplation of lysine 2,3-aminomutase from other species, as well as variants of such lysine 2,3-aminomutases and the use of such enzymes to prepare β-lysine, does not sufficiently describe the claimed genus of methods of use of any protein having lysine 2, 3-aminomutase activity. Applicants disclosure of the species of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, and 16 does not put applicants in possession of all possible lysine 2,3-aminomutases and thus applicants were not in possession of the claimed methods of use of all possible lysine 2,3-aminomutases.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Newly amended claims 49-51 are rejected under U.S.C. 112, first paragraph because the recitation "containing purified lysine2,3-aminomutase **other than that from Clostridium subterminale SB4**" is not supported by the original specification at the time of filing. While applicants disclosure of a number of lysine 2,3-aminomutase from species other than Clostridium subterminale SB4, is acknowledged applicants do not have support for the claimed genus of methods comprising the use of those lysine 2,3-aminomutase from species other than that from Clostridium subterminale SB4.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30, 38 and 39 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chirpich et al. I (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS).

As previously stated, Chirpich et al. I teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-β-lysine from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*).

Claims 30, 38 and 39 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chirpich et al. (Preparative Biochemistry. Vol. 3, No. 1, pp. 47-52, 1973, See PTO-892, ref U).

As previously stated, Chirpich et al. II teach the preparation of L- -lysine from L-lysine comprising incubating L-lysine in a solution containing lysine 2,3-aminomutase from lysine-fermenting *clostridia* followed by the isolation/separation of L-b-lysine by differential elution. As the preparation yielded 123 millimoles or 61% based on the initial amount of lysine all cofactors required for lysine 2,3-aminomutase activity were present for the reaction.

Each of the above rejections rejection were originally stated in the previous office action and repeated below for applicants convenience. Applicants have referred to the

first Chirpich et al. reference used above as Chirpich et al. I and the second as Chirpich et al. II. and applicants appear to argue these rejections together. The reference to each of the two different Chirpich et al. references will be maintained as discussed below.

In response to these rejections applicants have amended claim 30 and traverse the rejections as they apply to the amended claims. Applicants submit that applicants invention as defined by claim 30 distinguishes over Chirpich et al. by reciting a method of producing L-β-lysine, using a substantially pure lysine 2,3-aminomutase, as defined by applicants on page 4, lines 19-22, and that Chirpich et al. I does not teach a substantially pure lysine 2,3-aminomutase. Applicants assert that the enzyme activity isolated by Chirpich et al. I was not substantially pure lysine 2,3-aminomutase as defined by applicants disclosure. Applicants support this assertion by submission of a declaration by Frank Ruzicka and Appendix A.

Applicants traversal is not found persuasive based on the following. Applicants specification states that **substantially pure** means that the desired purified protein is essentially free from contaminating cellular components, as evidenced by a single band following polyacrylamide-sodium dodecyl sulfate gel electrophoresis (SDS-PAGE). The term "substantially pure" is further meant to describe a molecule which is homogeneous by one or more purity or homogeneity characteristics used by those of skill in the art. The lysine 2,3-aminomutase taught by Chirpich et al. I was 95% homogeneous on the basis of disc gel electrophoresis and gel filtration, thus the lysine 2,3-aminomutase taught by Chirpich et al. I is encompassed by "a molecule which is homogeneous by

one or more purity or homogeneity characteristics used by those of skill in the art". Applicants submission that a preparation of *Clostridial terminale* SB4 lysine 2,3-aminomutase from cell extract prepared by a modification of the method of Chirpich et al. I used, resulted in at least 5 other proteins on the SDS-PAGE presented by applicants in Appendix A, as well as applicants submission that the major band was not more than 75% pure is acknowledged however not found persuasive for the following reasons. First applicants state that the preparation that applicants analyzed in Appendix A was not in fact prepared by the method of Chirpich et al. I, but rather by applicants modification of the method of Chirpich et al. I. Thus it remains in question the effect of applicants "improvements" of the method of Chirpich et al. I.

Further applicants present a comparison of applicants "modified Chirpich et al. I lysine 2,3-aminomutase preparation" and "applicants lysine 2,3-aminomutase preparation" and draw the conclusion that applicants preparation of lysine 2,3-aminomutase meets the above discussed definition of substantially pure, while that of Chirpich et al. I does not. This is not persuasive based on the clearly different amounts of protein loaded in each the lanes of the SDS-PAGE. Applicants statements that the modified preparation of Chirpich et al. I contained at least 5 other proteins (presumably based on the presence of at least 5 additional bands) and that applicants preparation displays essentially a single band (presumably based on the absence of additional bands) is not found persuasive based on the different levels of protein that appears to have been loaded into each lanes of the appendices gel. As it appears that much less protein was loaded for applicants preparation, the level of additional bands would be

equally less and thus applicants arguments that the applicants preparation meets the definition of "substantially pure" as discussed above, but that of Chirpich et al. does not is not found persuasive. Based on the above, the preparations of Chirpich et al. I, applicants modification of preparation of Chirpich et al. I and applicants preparation of lysine 2,3-aminomutase are each considered to be encompassed by applicants definition of "substantially pure" or at the very least it is believed that applicants cannot differentiate applicants preparation from the preparation of Chirpich et al. I based on this definition as discussed above. Thus applicants traversal of each of the rejections over Chirpich et al. are not found persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 37, 42, 43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chirpich et al. (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS).

As previously discussed, Chirpich et al. teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-β-lysine

from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*). Chirpich et al. teach that their purification method is more effective than that which was previously reported.

One of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for further use in the recombinant production and characterization of lysine 2,3-aminomutase. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al., which would involve the isolation of L-β-lysine from the cultured cells. The reasonable expectation of success comes from the high degree of knowledge in the art with respect to the isolation and recombinant expression of the genes which encode previously isolated proteins as well as the teachings of the isolation of the lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al. The reasonable expectation of success comes from the high degree of knowledge in the art with respect to the isolation and recombinant expression of the genes which encode previously

isolated proteins as well as the teachings of the isolation of the lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al.

Applicants traverse this rejection on the basis that the Examiner has not established a prima facie case of obviousness. Applicants further submit Chirpich et al. I does not teach a single element of applicants invention as defined by claim 29. In response to this applicants are reminded that this is an obviousness rejection, not a rejection based on anticipation. Applicants further submit that the examiner has failed to show any suggestion or motivation to make the claimed invention, but rather has put forth an obvious to try rationale. Applicants argument is not found persuasive because as previously stated, Chirpich et al. teach the claimed method using naturally produced lysine 2,3-aminomutase.

As previously stated, one of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for further use in the recombinant production and characterization of lysine 2,3-aminomutase. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Any method of recombinantly

expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al., which would involve the isolation of L-β-lysine from the cultured cells.

In response to applicants comments as to whether it is obvious to produce L-β-lysine by the claimed methods, as previously stated, any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al., which would involve the isolation of L-β-lysine from the cultured cells, making obvious the claimed methods.

Applicants comments regarding the purity of the preparation of Chirpich et al. have been addressed above under the 102 rejection, although applicants are reminded that this rejection is not based on anticipation, but rather obviousness and the production of a protein produced recombinantly would result in an increased purity of the produced protein relative to the naturally produced protein for the reasons previously discussed.

Applicants comments regarding the necessity of more then one protein for lysine 2,3-aminomutase activity are acknowledged, however not found persuasive on the basis that Chirpich et al. teach that the activity of lysine 2,3-aminomutase migrates and appears as a single peak/band in their experiments. The amount of time that has passed since the publication of Chirpich et al.'s articles and the present application is acknowledged but not seen as relevant as to a measure of the motivation to make the claimed invention.

Claims 40 and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chirpich et al. (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS) as applied to claims 29, 37, 42, 43 and 45 above, further in view of Rozzell (U.S. Patent No. 4,88,0738), and Kusumoto et al. (Tetrahedron Letters, Vol 23, No. 29, pp 2961-2964).

The rejection was stated in the previous office action, and repeated below for applicants convenience.

As discussed previously, Chirpich et al. teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-β-lysine from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*). Chirpich et al. teach that their purification method is more effective than that which was previously reported.

Kusumoto et al. teach the synthesis of the antibiotic streptothricin F comprising adding β-lysine, carbamoyl and streptolidine moieties to the gulosamine molecule. Kusumoto et al. further teach that this synthesis method makes it possible to synthesize structural analogs of streptothricin which are necessary for the future studies of the relationship between structure and activity of the streptothricin antibiotic.

Rozzell teaches the biocatalytic methods for producing a desired amino acid using purified or partially purified enzymes either in solution or as immobilized enzymes.

One of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al., to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for use in the recombinant production lysine 2,3-aminomutase. One would have been further motivated to immobilize the recombinantly expressed lysine 2,3-aminomutase for use in a method of producing L-β lysine for use in the synthesis of the antibiotic streptothricin and streptothricin analogs, so that the enzyme could be used repeatedly in a process of synthesizing L-β-lysine. Further it is known in the art that enzyme immobilization is a means of stabilizing the enzyme and thus increasing the amount of L-β-lysine that is produced per lysine 2,3-aminomutase molecule/protein. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al. which would involve the isolation of L- -lysine from the cultured cells. The reasonable expectation of success comes from the high degree of knowledge in the art with respect to the isolation and recombinant expression of the genes which encode previously isolated proteins.

In response to this rejection, applicants continue to traverse as above that the cited art fails to teach the use of a substantially pure lysine 2,3-aminomutase. This is not found persuasive for each of the reasons discussed above, and as applicants have been reminded this is not a rejection based on anticipation, but rather on obviousness.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as previously stated, one of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al., to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for use in the recombinant production lysine 2,3-aminomutase.

One would have been further motivated to immobilize the recombinantly expressed lysine 2,3-aminomutase for use in a method of producing L-β lysine for use in the synthesis of the antibiotic streptothricin and streptothricin analogs, so that the enzyme could be used repeatedly in a process of synthesizing L-β-lysine. Further, it is known in the art that enzyme immobilization is a means of stabilizing the enzyme and

thus increasing the amount of L-β-lysine that is produced per lysine 2,3-aminomutase molecule/protein.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
1/5/2003